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FORMULATION AND EVALUATION OF TASTE-MASKED BERBERINE CHLORIDE FOR ORAL SUSPENSION USING SOLID LIPID DISPERSION

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Summary

Formulation and Evaluation of Taste-Masked Berberine Chloride for Oral Suspension Using Solid Lipid Dispersion

This study was focused on the formulation and evaluation of taste-masked berberine chloride (BC) applied for oral suspension. In this research, stearic acid (SA) was utilized as a carrier which played a significant role as a barrier to prevent the release of drugs in the oral cavity. The results revealed that Eudragit EPO (EE) could be utilized as a channeling agent besides the taste masking characteristic. The optimal ratio of BC:SA:EE was 2:10:1. The microparticles were then mixed into ethanol containing EE and Aerosil. The dissolution profile of BC from microparticles showed the release of over 70% of BC content within 45 minutes. Differential Scanning Calorimetry (DSC) revealed the physical states of the system. The excipient-drug interactions were not detected on infrared spectroscopy (IR). Additionally, lipid-matrix microparticles had a palatable taste with high dissolution, and good flowability which can be adapted for oral suspension preparation.

Keywords: *Berberine chloride, Taste masking bitter, Lipid, Oral suspension.*

1. Introduction

Berberine, a quaternary protoberberine isoquinoline alkaloid, is a well-known naturally occurring medicine derived from the root and the stem bark of numerous clinically crucial medicinal plants [1], and has an array of pharmacological characteristics including antimicrobial, antiprotozoal, antidiarrheal and anti trachoma activity [2]. However, it has an intensely bitter taste, which makes it difficult for oral administration to some special populations like pediatrics and geriatrics as it could not be adjusted by flavor or sweetener adjuncts.

Some other studies on taste masking of BC have been reported. Hong Jiang et al. applied powder surface modification technology is an attempt to mask the bitterness of BC by changing the surface properties in vibromill. Mannitol was chosen as the best modifier, and the optimal ratio of BC and mannitol was 6:4 with grinding together for 2 min in vibromill [3]. Xuelian Hu et al. prepared taste-masked microcapsules of BC for orally disintegrating tablets. Ber powder was forced through a 100-mesh sieve to remove large particles. The sieved powder was granulated with 3% (*w/w*) hydroxypropylmethylcellulose (HPMC) aqueous solution using the side-spray method in a fluidized bed. The operating conditions were as follows: inlet air temperature was 75 - 80°C, sample temperature was 54 - 60°C, spray pressure was 0.1 MPa, diameter of the spray nozzle was 1.2 mm, flow rate was 3.2 - 6.4 mL/min, and disk rotation speed was 160-200 rpm. The drug load was 800 g and the time of granulation was about 3 h. After granulation, the resultant granules were removed from fluid bed and the fluid bed chamber was cleaned thoroughly. Then the granules were coated with 8% Eudragit E100 alcohol solution in the fluidized bed. The operating conditions were as follows: inlet air temperature was 40 - 45°C, sample temperature was 35 - 40°C, spray pressure was 0.1 MPa, the diameter of the spray nozzle was 1.2 mm, and the flow rate was 3.2 - 8 ml/min. The duration of the coating process was variable depending on the drug to Eudragit ratio and it was about 8 h when the ratio was 1:0.8. The median diameter was 105 µm before coating and 145 µm after. The entrapment efficiency of Ber microcapsules was found to be 82.8% with a drug loading of 55.0%. The dissolution profiles showed that Ber microcapsules dissolved more than 50% within 5 min when placed in 0.1 mol/l HCl but only 0.56% within 20 min in purified water. These results suggested that after being coated with Eudragit E100, Ber was released hardly in the saliva [4]. Chenguang Wang et al. formed salts with the sweeteners acesulfame and saccharine, through the anion exchange reaction. Both salts also exhibit reduced aqueous solubility, which further alleviates the problem of bitter taste of the drug by limiting the dissolution of berberine [5].

Quite a few researches were reported where the bitter drug was incorporated within or coated with lipid carriers including glycerol distearate, stearic acid, hydrogenated oil, lecithin, and glyceryl monostearate to achieve taste masking [6],[7]. In this study, solid lipid dispersion was applied to address the overwhelming bitterness of berberine chloride (BC) using stearic acid as a taste mask carrier. Besides that, the influence of incorporated lipids on the drug release behavior and further on taste masking was also investigated.

2. Materials and Methods

2.1. Materials

Berberine chloride (BC) was obtained from Ningbo Loncin Biotechnology Co. Ltd., China and conformed with the specification monograph of Chinese Pharmacopoeia 2020. BC reference

substance (purity: 98.06%, CAS number: 633-65-8) was purchased from Sichuan Weikeqi Biological Technology Co., Ltd. China. Stearic acid (SA) was purchased from Shandong Huashiyuan New Material Co., Ltd., China. Eudragit EPO (EPO) was provided as a gift sample by Evonik, Germany. Aerosil was provided as a gift sample by Cabot Sanmar Limited, Tamil Nadu, India. Dibasic potassium was purchased from Merck Specialities Pvt. Ltd., Mumbai, India. Hydrochloric acid (HCl) was purchased from Fisher Scientific, Mumbai, India. Acetonitrile (ACN) and trifluoroacetic acid (TFA) were obtained from Merck, Germany. All other chemicals and solvents used were of analytical grade. Double distilled water was provided by the National Institute of Medicinal Materials.

2.2. Methods

2.2.1. Preparation of taste-masked BC microparticles by solid dispersion:

The accurately weighed amount of SA (quantity based on the batches designed) was placed in a porcelain dish and melted over a thermostatically controlled water bath at 80°C. When a uniform molten mass was obtained, the accurately weighed amount of BC (**Table 1**) and Eudragit EPO, if used, was added to the melted lipid and mixed with a glass rod. When all the BC was incorporated, the molten mass was allowed to cool to room temperature. The resulting congealed mass was sifted manually by passing through a sieve of 125 and 250 µm to obtain the matrix microparticles. Various compositions and sizes of the prepared BC-incorporated lipid-matrix microparticles were given in **Table 1.**

2.2.2. Assay of drugs loading:

A variable amount of granules, theoretically equivalent to 50 mg of berberine chloride was accurately weighed and 40 mL of methanol was added and the mixture was sonicated for 30 minutes in an ultrasonic machine for extraction. Finally, the solution was transferred to a 50 mL volumetric flask and replenished with methanol for sufficient. Dilute the solution to the appropriate ratio with MeOH. The solution was filtered through a 0.45 µm filter prior to injection in HPLC system. The drug content was determined using the standard calibration curve developed with the concentration ranging from 20 to 400 µg/ml.

***HPLC conditions*:** Mobile phase: Acetonitrile and *Solution A* (45:55) (Solution A: Dissolve 1mL of trifluoroacetic acid (TFA) in water, dilute with water to 1000 mL, mix, filter, and degas). Chromatography system: VertiSep UPS C_{18} HPLC COLUMN C_{18} (4.6 x 250 nm, 5 µm); flow rate: 1.1 mL/min; injection volume: 5 µL; detector: UV 346 nm. Identify the retention times of the peaks corresponding to berberine chloride. The percentages of BC loading were calculated in the samples taken:

$$\text{Result (\%)} = \frac{Ru \times Cs \times V \times n \times 100}{Rs \times W \times (100 - B)}$$

Where: Ru, Rs is *the* peak area of the relevant analysis from the *Sample solution* and peak area of BC from the *Standard solution,* respectively. Cs (mg/mL) is *the* concentration of BC RS in *Standard solution* (mg/mL); V is the volume of the *Sample solution* (mL); W is the weight of the sample taken to prepare the *Sample solution* (mg) and B is moisture content of sample; n is dilution factor.

2.2.3. *In vitro* taste masking assessment:

The taste masking ability of preparation was examined by *in vitro* assessment where a delayed drug release from the matrix in early 1 min was considered as the main *in vitro* parameter for successful taste masking. Lipid-matrix microparticles, equivalent to 50 mg of BC were accurately weighed on an electronic digital balance, and placed in a volumetric flask containing 10 ml phosphate buffer pH 6.8 and stirred for 1 min with the rotation of 1000 rpm. The mixture was filtered and diluted with MeOH, and then the filtrate was analyzed for BC concentration at 346 nm by the HPLC system. BC released in the phosphate buffer pH 6.8 (simulated saliva) was compared to the threshold bitterness concentration of BC.

2.2.4. *In vitro* dissolution studies:

Evaluation of *in vitro* dissolution of berberine chloride from microparticles was performed using paddle apparatus Pharmatest DT 70 dissolution (Germany) containing 900 ml of 0.1 N HCl solution (pH 1.2) as the dissolution media, the speed of paddle was set up at 100 rpm. The matrix microparticles were placed in a dissolution medium maintained at 37 ± 0.5°C. 10 ml of dissolution samples were withdrawn to determine the percentage of BC release in each formula at the interval of 5, 10, 15, 30, 45, 60, 90, and 120 minutes and the dissolution medium was replenished immediately with the same volume of fresh solution to maintain an ideal sink condition. Samples were filtered through a membrane filter of 0.45-µm prior to HPLC analysis, discarding the first few mL of the filtrate. Each study was triplicated.

For the comparison of the dissolution profiles, the similarity factor (f_2) should be estimated by using the following formula:

$$f_2 = 50 \times log\left\{\left[1 + \frac{1}{n}.\sum_{t=1}^{n}(R_T - T_T)^2\right]^{-0.5} \times 100\right\}$$

Where as f_2 is the similarity factor, n is the number of time points, R(t) is the mean percent reference drug dissolved at time t after initiation of the study and T(t) is the mean percent test drug dissolved at time t after initiation of the study. The f_2 value from 50 to 100 indicated that the difference of dissolution rates were considered unsignificantly.

2.2.5. Drug release kinetics:

Data obtained from the *in vitro* drug release study was analyzed by different kinetic models and fitted into corresponding equations in order to evaluate the release mechanism of BC from the lipid - matrix granules. The kinetic models used were represented by the following Eqs. (1)-(5): Zero order model: $Q_t = Q_o + K_o t$ (1); First order model: $\log Q_t = \log Q_o + K_1 t/2{,}303$ (2); Higuchi model: $Q_t = K_h \sqrt{t}$ (3); Hixson and Crowell cube root model: $W_o^{1/3} - W_t^{1/3} = K_s t$ (4); Korsmeyer and Peppas model: $M_t/M_\infty = Kt^n$ (5) where Qt and Mt refer to amount of the drug release at time t, Q_0 is the initial amount of drug present at time equal to zero, W_t and W_0 represents the amount of the drug at zero and t, M_1 is the amount of drug dissolved at infinite time. The terms K_0, K_1, K_h, K_s, and K were the release kinetic constants for zero-order, first-order, Higuchi, Hixson Crowell and Korsmeyer and Peppas model. The model fitting using Eqs. (1) - (5) was done with DDSolver [6].

2.2.6. Surface morphology of lipid-matrix microparticles:

The surface characteristics of lipid-matrix microparticles were studied with a scanning electron microscope (Hitachi S - 4800, Japan). The samples were scanned at 5 kV voltage and photographed at a magnification of 230 and 1600.

2.2.7. Physical state of BC in lipid-matrix:

Differential scanning calorimetry (DSC) thermograms were recorded using a scanning calorimeter (NETZSCH DSC 204F1 Phoenix 240-12-0416-L, Germany) to characterize the thermal properties of BC and SA and Eudragit EPO also to investigate the physical state of BC in the lipid matrix granules. Samples (2-5 mg) were placed in a flat bottomed aluminum pan and heated at a constant rate of 10°C/min. The samples were scanned from 35 to 250°C.

2.2.8. Fourier transformation infrared spectroscopy (FT-IR):

FT-IR spectra of the powder samples collected using a high resolution FT-IR spectrometer (Spectrum Two™, PerkinElmer). For each sample, 32 scans were averaged. IR data in the range of 4000-600 cm^{-1} at a resolution of 4 cm^{-1} were processed using OPUS software.

All experiments were repeated in triplicate. The data were presented as the means ± SD (standard derivation) and analyzed by Microsoft excel 2019.

3. Results and Discussion

3.1. Formulation, in vitro taste assessment and dissolution

Table 1. Compositions and characteristics of lipid microparticles prepared by solid dispersion (means ± SD, n=3)

Batch	Size (µm)	BC (g)	SA (g)	EE (g)	Drug assay (%)	*In vitro* taste assessment (conc. (µg/ml)
BC	-	-	-	-	97.25 ± 5.88	1845.17 ± 22.82
F1	0-125	5	20	-	20.29 ± 0.26	1263.56 ± 14.15
F2	125-250	5	20	-		1436.07 ± 12.06
F3	0-125	5	25	-	18.68 ± 0.39	**1088.14 ± 12.27**
F4	125-250	5	25	-		1151.19 ± 18.03
F5	0-125	5	30	-	15.61 ± 0.19	810.56 ± 5.84
F6	125-250	5	30	-		1161.18 ± 34.08
F7	0-125	5	25	0,5	15.41 ± 1.12	588.70 ± 9.36
F8	0-125	5	25	1,25	15.59 ± 0.24	642.26 ± 13.17
F9	**0-125**	**5**	**25**	**2,5**	**14.47 ± 0.18**	**626.94 ± 12.75**
F10	0-125	5	25	5	14.50 ± 0.30	847.17 ± 8.78

Due to medical ethic regulatory when testing in animals or human, the taste masking ability of BC lipid matrix granules was determined by *in vitro* drug release test as none of the excipient incorporated in taste masked BC granules was having bitter taste. It is only the BC which is contributing bitter feel to the formulation. Hence, *in vitro* drug release test could be a good surrogate for taste assessment, especially for this type of formulation where drug release is prevented or delayed in the oral cavity by embedding the drug in hydrophobic matrix. BC bitterness in drug release medium was evaluated by measuring drug release and comparing it with bitterness threshold concentration. A corresponding between taste evaluation and the drug concentration has been reported in previous publication [3], which was correlated with *in vitro* drug release at initial time points for the purpose of bitterness evaluation. *In vitro* taste assessment of all the prepared batches (**F1-F10**) were carried out to determine the release of BC at 1 min in phosphate buffer pH 6,8 (**Table 1**). The larger the size, the higher the coating capacity of the carrier that leads to the reduction of surface area and the poorer contact of the drug with the dispersion medium (DM), so the concentration of BC after dispersion is lower. Microparticles of size ranged from 125 to 250 µm had a lower concentration in DM (from 1161.18 to 1436.07 µg/ml) compared to the raw material (1845.17 µg/ml) but felt gritty when swallowing. To meet the requirements of preparing oral suspension, the study selected microparticles with size below

125 µm. However, increasing the lipid ratio did not significantly reduce the BC concentration in DM, and simutaneously affected the solubility of the active substance because the hydrophobic properties of the lipids made it difficult to release the API. After 45 min, the dissolution of BC was all below 75%, which raised the requirement for improved BC solubility from microparticles, but met the requirements for preparation to reduce bitterness. **F3** formulation was selected for further studies. **F7, F8, F9, F10** were prepared to evaluate the role of Eudragit EPO, a terpolymer based on N,N-dimethylaminoethyl methacrylate with methylmethacrylate and butylmethacrylate which can be dissolve in pH below 5 thus leading to prevent BC release in oral cavity. Furthermore, this polymer can be simutenously dissolved with SA. This can create channels, pores which contribute to the diffusion of BC in dissolution medium then enhance dissolution. **F9** formulation had a good *in vitro* taste assessement and dissolution after 45 min. Beside that f_2 factor between **F9** and **F3** and BC were 13,18 and 52,42, respectively showed that there was unsignificant difference in dissolution between taste-masked microparticle and raw materials. In order to evaluate the formation of pores, BET method was carried out in order to estimate the pore volume between **F3** and **F9** formulation. The results showed that they were 0,00939 and 0,1172 cm^3/g for **F3** and **F9**, respectively. Utilizing Eudragit EPO not only reduce the diffusion of BC in oral cavity but also enhance its dissolution. Then **F9** fomulation was mixed with 5% EE in 1ml EtOH and Aerosil, the mixture was sieved though 0,125 mm to obtain taste-masked microparticle with BC concentration in DM of 289,87 µg/ml which was reduced by more than 6 times in the comparison with raw material.

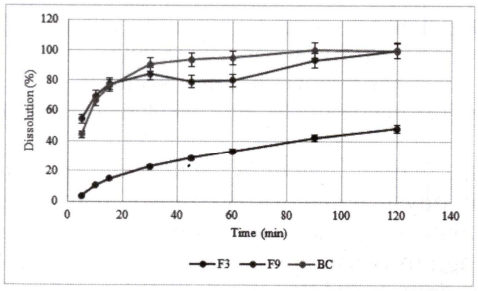

Fig. 1. *In vitro* drug release of **F3**, **F9** and **BC**

Table 2. Dissolution of berberine chloride from lipid microparticles (means ± SD, n=3)

Time (m)	5	10	15	30	45	60	90	120
F1	20.53 ± 0.23	34.62 ± 0.39	44.20 ± 0.50	66.36 ± 0.74	**75.57 ± 0.85**	81.92 ± 0.92	90.31 ± 1.01	97.94 ± 1.10
F2	8.33 ± 0.52	9.50 ± 0.25	9.93 ± 0.27	21.19 ± 0.57	**38.27 ± 1.03**	46.83 ± 1.26	47.07 ± 1.26	51.96 ± 1.39
F3	**3.68 ± 0.17**	**10.44 ± 0.11**	**14.76 ± 0.16**	**22.93 ± 0.25**	**28.62 ± 0.31**	**33.09 ± 0.36**	**42.29 ± 0.46**	**48.30 ± 0.52**
F4	5.51 ± 0.23	6.15 ± 0.14	6.86 ± 0.16	10.46 ± 0.24	**18.71 ± 0.42**	26.27 ± 0.59	32.73 ± 0.74	37.13 ± 0.84
F5	4.59 ± 0.23	7.10 ± 0.38	10.77 ± 0.58	35.43 ± 1.91	**44.73 ± 2.42**	51.98 ± 2.81	58.61 ± 3.16	64.10 ± 3.46
F6	7.27 ± 0.12	8.71 ± 0.09	9.54 ± 0.10	38.18 ± 0.39	**46.64 ± 0.48**	50.93 ± 0.52	56.02 ± 0.58	57. 18 ± 0.59
F7	18.01 ± 0.22	38.86 ± 0.93	50.21 ± 0.60	57.11 ± 1.43	**64.69 ± 2.72**	65.09 ± 1.19	73.96 ± 0.38	73.43 ± 1.41
F8	36.97 ± 0.67	45.71 ± 1.14	51.75 ± 2.34	61.58 ± 0.94	**63.57 ± 0.66**	73.04 ± 1.02	74.58 ± 1.93	78.59 ± 3.14
F9	**54.38 ± 0.08**	**69.45 ± 1.07**	**77.40 ± 3.54**	**84.32 ± 1.50**	**79.20 ± 2.06**	**79.96 ± 2.33**	**93.37 ± 1.42**	**99.68 ± 1.26**
F10	12.52 ± 0.19	26.22 ± 0.40	38.93 ± 1.62	54.43 ± 1.13	**57.40 ± 1.85**	58.32 ± 1.16	60.29 ± 0.70	61.19 ± 1.25
BC	**44.30 ± 0.83**	**66.50 ± 1.25**	**76.23 ± 1.43**	**90.58 ± 1.70**	**93.70 ± 1.76**	**94.96 ± 1.79**	**100.13 ± 1.88**	**100.00 ± 1.88**

3.2. Drug release kinetics

Table 3. Kinetic models of **F9**

Model	AIC value	R^2	Equation of kinetics
Zero-order	75.41	0.87	$F(\%) = 0{,}981 \times t$
First order	62.85	0.99	$F(\%) = 100 \times [1 - e^{-0{,}052 \times t}]$
Higuchi	64.90	0.95	$F(\%) = 9{,}708 \times t^{0.5}$
Hixson-Crowell	66.20	0.99	$F(\%) = 100 \times [1 - (1 - 0{,}011 \times t)^3]$
Korsmeyer-Peppas	**35.77**	**0.98**	$\mathbf{F(\%) = 35{,}720 \times t^{0.183}}$

Drug release kinetic analysis was applied to the *in vitro* drug dissolution data of **F9**. The values of different drug release parameters including determination coefficient (r^2), release rate constants (K), and AIC obtained from lipid-matrix granules were shown in **Table 3**. The best fit of the dissolution data was investigated based on the highest magnitude of determination coefficient and lowest AIC values and appears to follow the **Korsmeyer-Peppas** model (coefficient: 0.98) and the AIC value is 35.77.

3.3. Surface morphology of lipid-matrix granules

The lipid-matrix microparticles (**F9**) were characterized by scanning electron microscopy (SEM) and photographs of lipid formulations at different magnifications were shown in **Fig. 2.** The SEM pictures of BC were in crystal shapes with angular structure, and the microparticles were covered with smooth surface lipids. This helps to explain the role of lipids covering the surface of BC particles thus limiting BC release to reduce bitterness.

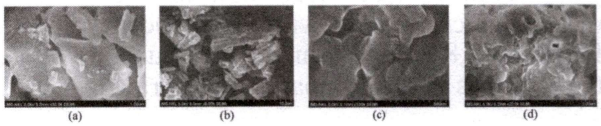

Fig. 2. SEM pictures (a): raw material (×30.0k), (b): raw material (×5.00k) (c): taste-masked microparticles và (d): microparticles after dissolution (×20.0k)

3.4. Physical state of BC in lipid-matrix granules

The physical state of BC in SA matrix granules was also examined by DSC techniques. The thermogram of BC, physical mixture and the lipid-matrix granules (**F9**) was depicted in **Fig. 3.** The DSC thermogram of BC shows three endothermic peaks at 56.8°C, 92.2°C and 192.2°C, corresponding to it melting points and an exothermic peak at 207.4°C related to the decomposition temperature of API. The DSC curve of the physical mixture showed a transition peak at 60.3°C corresponding to its melting point and got shifted to a higher temperature at 99.4°C. However, it was observed that the taste-masked microparticles (**F9**) showed only an endotherm peak corresponding to the melting point of SA at 55.7°C. This suggests that BC might be dissolved in the lipid matrix to form the solid dispersion. The DSC determined the physical state transformation of BC in lipid-matrix **F9** formulation.

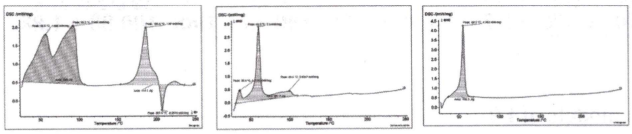

Fig. 3. DSC diagram of BC, physical mixtures, and taste-masked microparticles

3.5. Fourier transformation infrared spectroscopy (FT-IR)

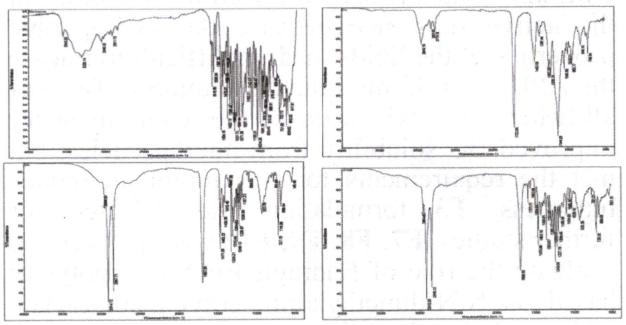

Fig. 4. FT-IR diagram of BC, Eudragit EPO, SA, and microparticles

On the FT-IR spectrum of BC appear characteristic absorption peaks (C-O = 1103 and 1271 cm^{-1}), (C = aromatic C = 1422 and 1619 cm^{-1}), (C-H = 2911 cm^{-1}). The FT-IR spectrum of Eudragit EPO appears to have a characteristic absorption peak for the ester group at 1144 and 1267 cm^{-1}, and an absorption band for the carbonyl group at 1722 cm^{-1}. In addition, there are the adsorption bands observed at 1387, 1453-1490, and 2949 cm^{-1} of the hydrocarbon chain. However, the most important signals were at 2770 and 2821 cm^{-1}, demonstrating the presence of the DMEA (dimethylethanolamine) functional group in the polymer. The FT-IR spectra of SA appear characteristic absorption peaks at 2914 and 2841 cm^{-1} which are characteristic of the $-CH_2-$ group, and an absorption peak at 1697 cm^{-1} which is characteristic of the carboxyl group -COOH. On the FT-IR spectrum of the microparticle sample, there are also characteristic absorption peaks at 2954, 2915, 2848, 1698, bands 1463-1506, 1249, and 1186 similar to the microparticle components, proving that the microparticles have no excipient interactions.

4. Conclusion

This paper was studied the preparation method to reduce berberine bitterness by solid dispersion system using lipid carrier and evaluated the microparticle characteristics, suitable for the preparation of oral suspension.

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